STUDY TITLE

Dow AgroSciences' Response to US EPA's Benfluralin Registration Review Docket EPA-HQ-OPP-2011-0931

DATA REQUIREMENT

None

AUTHORS

A. K. Hudson, S. Knowles, and S. McMaster

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Dow AgroSciences LLC
9330 Zionsville Road
Indianapolis, IN 46268

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Company: Dow AgroSciences LLC

Company Agent: A. K. Hudson

Title: Regulatory Manager

Signature: Amy Hudson

Date: 2/21/12

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STATEMENT OF COMPLIANCE WITH GOOD LABORATORY PRACTICE STANDARDS

Title: Dow AgroSciences' Response to US EPA's Benfluralin Registration Review Docket EPA-HQ-OPP-2011-0931

Compound: Benfluralin

This report does not meet the definition of a GLP study as it appears in:

United States Environmental Protection Agency
Title 40 Code of Federal Regulations Part 160
Federal Register, 17 August 1989

Organization for Economic Cooperation and Development
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NON-GLP STUDY

Amy Hudson — 2/21/12

A. K. Hudson
Sponsor
Dow AgroSciences LLC

Date

Amy Hudson — 2/21/12

A. K. Hudson
Submitter
Dow AgroSciences LLC

Date

Amy Hudson — 2/21/12

A. K. Hudson
Study Director/Author
Dow AgroSciences LLC

Date

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NON-GLP STUDY

SIGNATURE PAGE

Amy Hudson Date 2/21/12

A. K. Hudson
Author
Dow AgroSciences LLC

Steve Knowles (NB) Date 2/21/12

S. Knowles
Co-author
Dow AgroSciences LLC

Steve A. McMaster Date 2/21/12

S. McMaster
Co-author
Dow AgroSciences LLC

TABLE OF CONTENTS

I. SUMMARY

As requested by the US EPA (EPA or the Agency), Dow AgroSciences (DAS) is providing comments to the Agency's documents contained in the initial docket for Registration Review for Benfluralin (EPA-HQ-OPP-2011-0931) which opened on December 21, 2011. These comments are intended to address errors and inconsistencies found in the following EPA documents: 1) Benfluralin Summary Document Registration Review: Initial Docket December 2011 (EPA-HQ-OPP-2011-0931-0002); 2) EFED Registration Review – Preliminary Problem Formulation for Benfluralin (EPA-HQ-OPP-2011-0931-0003); and 3) Benfluralin: Registration Review Scoping Document for Human Health Assessments (EPA-HQ-OPP-2011-0931-0004). DAS appreciates the opportunity to review the initial docket prepared for Phase One of the registration review process for benfluralin and submits comments regarding assessments and data requirements.

II. INTRODUCTION

DAS is providing comments to the Agency based on the review of documents contained in the initial docket for Registration Review for Benfluralin (EPA-HQ-OPP-2011-0931) which opened on December 21, 2011. Documents which have been reviewed for comments in this report include: 1) Benfluralin Summary Document Registration Review: Initial Docket December 2011 (Summary Document) [1]; 2) EFED Registration Review - Preliminary Problem Formulation for Benfluralin (EFED Review) [2]; and 3) Benfluralin: Registration Review Scoping Document for Human Health Assessments (HED Review) [3]. DAS comments include error correction, requests for clarification, differences in data interpretation, presentation of some additional information, and views regarding the need for new studies.

Benfluralin is a highly effective herbicide that has been used for over 40 years for the control of economically important annual grasses and broadleaf weeds in many countries around the world. It is a dinitroaniline herbicide with a microtubule assembly inhibitor mode of action. Benfluralin has several unique characteristics that make it a critical component in weed management for many important crops. For example, it is a soil-applied herbicide with both grass and broadleaf weed activity on a wide variety of species. In addition, above ground portions of crops have no residues following treatment. Benfluralin is used as the foundation of integrated weed management programs and provides a different mode of action to control weeds that are becoming resistant to other commonly used herbicides. It remains a highly cost effective and key weed control tool, particularly for certain specialty crops.

A. Key Features of Benfluralin

Benfluralin is an herbicide for the pre-emergence control of annual grasses and broadleaf weeds. It provides unsurpassed control of many economically important annual grasses including foxtail species (*Setaria* sp.), seedling johnsongrass (*Sorghum halapense*), and small seeded broadleaf weeds including pigweed (*Amaranthus* sp.) and common lambsquarters (*Chenopodium*). Because benfluralin is primarily used as a pre-emergence herbicide, it is often referred to as a foundation treatment. Foundation herbicides are used to protect yield potential in the early stages of crop

development from weed competition for moisture, nutrients and sunlight. This protection is particularly important for small-seeded crops such as lettuce. Foundation herbicides provide benefits over post-emergent herbicides. Flexibility of application timing is important when growers face weather or other issues that may affect the timing of application. Benfluralin provides early season weed control and more flexibility with timing of the post-emergence treatments. In many cases, the use of a foundation treatment will eliminate the need for a second post-emergence treatment to clean up weed flushes or escapes.

B. Benefits of Benfluralin

Benfluralin provides low cost broad spectrum weed control including excellent grass control. It can be used in minimum tillage crop production systems. It also controls many of the ACCase, ALS, glyphosate, and triazine resistant weed species. Compared to other pre-emergence herbicides, benfluralin has several advantages that give it unique functionality. For instance, as benfluralin is incorporated after application, no rainfall is needed for activation. Because of its wide margin of crop selectivity, no crop injury will occur if heavy rains occur after application. Benfluralin can be applied in liquid sprays of water or on fertilizer. It can be tank-mixed or followed by overlay or post-emergence treatments with other herbicides to improve the spectrum of weeds controlled. Benfluralin controls weeds by disrupting growth processes during germination. It is a valuable alternative in weed resistance management programs which require the rotation of differing herbicide modes of action.

III. DAS COMMENTS ON THE AGENCY'S SUMMARY DOCUMENT

The comments in this section are organized in a "point-by-point response" format using the Agency's 19-page Summary Document as the basis. Please note that in several instances significant detail supporting the summary comments offered here is provided in subsequent sections of this report (see Sections IV and V).

A. Preliminary Work Plan

The Agency states on page 5 of 19:
"The Agency anticipates needing the following data for use in conducting a complete ecological risk assessment, including an endangered species assessment, for benfluralin:

Environmental Fate

- *Non-Guideline – Laboratory Volatility (Special Study)*

Ecological Effects

- *GLN 850.1300 – Aquatic Invertebrate Life – Cycle (Freshwater)*
- *GLN 850.2100 – Avian Acute Oral Toxicity Study (Passerine species)*
- *Non-guideline – Whole Sediment Chronic Invertebrates, Freshwater and Marine (Special Study)"*

DAS Comment:
Each of these potential study requirements is discussed on-by-one in Section IV of this report. In many cases, additional data are available to address them. All reports referenced within this document are available to the Agency upon request.

The Agency states on page 7 of 19:
"The toxicity and residue chemistry databases for benfluralin are complete except for the following studies, which the Agency anticipates requiring for use in conducting an updated human health risk assessment:

- *GLN 870.6200 – Acute and Subchronic Neurotoxicity*
- *GLN 870.7800 – Immunotoxicity"*

DAS Comment:
Each of these potential study requirements is discussed in Section V of this report.

B. Fact Sheet

The Agency States on Page 13 of 19:
"Target weeds include Johnson grass seedlings, chickweed, lambs quarters, purslane knotweed, clover, pigweed, plantain, crabgrass, foxtail, goose grass, Poa annua, barnyard grass, and fescue."

DAS Comments:
The following target weeds should be listed as one word: Johnsongrass, Lambsquarters, Goosegrass, and Barnyardgrass.

The Agency states on page 18 of 19:
"The following data remain outstanding:

- *GLN 850.1010 – Acute Toxicity Freshwater Invertebrates Study*
- *GLN 850.1025 – Oyster Acute Toxicity Test (Shell Deposition)*
- *GLN 850.1075 – Fish Acute Toxicity Test (Bluegill, Rainbow Trout)*
- *GLN 850.1500 – Fish Life Cycle*
- *GLN 850.2300 – Avian Reproduction Test (Bobwhite Quail)*
- *GLN 850.4100 – Seedling Emergence Terrestrial Plant Toxicity Test, Tier II*
- *GLN 850.4200 – Vegetative Vigor Terrestrial Plant Toxicity Test, Tier II*
- *GLN 850.5400 – Aquatic Plant Growth Tier II Study (Non-Vascular Aquatic Plant)*
- *GLN 870.3465 – 90-Day Inhalation Study (28-day duration acceptable)*
- *GLN 870.4200 – Mouse Carcinogenicity Study*
- *GLN 860.1200 – Directions for Use (modify labels to specify 12 month plant-back interval)*

DAS Comment:

Each of the following potential study requirements is discussed one-by-one in Section IV of this report: 850.1010, 850.1025, 850.1075, 850.1500, 850.2300, 850.4100, 850.4200, and 850.5400. Each of the following potential study requirements is discussed one-by-one in Section V of this report: 870.3465 and 870.4200.

IV. DAS COMMENTS ON THE AGENCY'S EFED REVIEW DOCUMENT

The comments in this section are organized in a "point-by-point response" format using the Agency's 103-page review document as the basis. Comments include error correction, requests for clarification, differences in data interpretation, presentation of some additional data, and views regarding the need for new studies as may be appropriate.

A. Stressor Source and Distribution

The Agency states on page 7 of 103:
"Benfluralin is applied as band treatment, broadcast, golf course treatment... soil incorporated treatment, and spray with ground or sprinkler irrigation systems."

DAS Comment:
Benfluralin products are not applied by ground or sprinkler irrigation systems. The only benfluralin product intended for application mixed with water is Balan DF. [4] This product label includes the specific prohibition: "Do not apply BALAN DF through any type of irrigation system." All other benfluralin containing products are solid, granule products and cannot be mixed in water for application.

The Agency states on page 7 of 103:
"All uses allow for ground and aerial applications...."

DAS Comment:
Benfluralin products are not applied by aerial application. The only benfluralin product intended for application mixed with water is Balan DF. [4] This product label includes the specific statement: "Spray Drift: Apply with nozzle height no more than 2 feet above the ground. Use hooded sprayer to direct spray toward the soil when wind speed is 10 mph or more at the application site. Use standard nozzles and apply as a medium or coarser spray (according to ASAE standard 572)." This statement precludes aerial application. All other benfluralin containing products are solid, granule products with a low concentration of benfluralin. These products are not conducive to aerial application nor are they applied in that manner.

The Agency states on pp. 8, 44, 51, 64, and 65 of 103:
Table 3.1 summarizes the benfluralin uses considered in Registration Review. Specifically, the site characterization entries include: Christmas tree plantations, turf, and non-agricultural rights of way/ industrial. (p. 8)

DAS Comment:
DAS disagrees with the Maximum Annual Rate or the Maximum Single Rate identified for Christmas Tree Plantations and Non Agricultural Rights of Way/Industrial site characterization in this table. In the Benfluralin RED, EPA requires that all product labels be amended to be eligible for re-registration. [5] A maximum of 2 pounds active ingredient per acre per application, maximum of 2 applications per year, and a maximum of 4 pounds active ingredient per acre per year were required for Christmas Tree Plantations and Non-Agricultural Rights of Way/Industrial sites. Additionally, Ornamental Sod Farm (Turf) was not a specific use pattern that was supported through the re-registration process. DAS requests that this table be amended to reflect the 2004 Benfluralin RED.

The Agency further states:
Appendix A is related to Table 3.1 and describes formulations and uses for benfluralin. Specifically, the site description entries include: Christmas tree plantations, industrial/ construction areas (outdoor), non-agricultural right of way/fencerows/ hedgerows, etc., and ornamental sod farm (turf). (pp. 44, 51, 64-65)

DAS Comment:
DAS agrees with the Agency summary in Appendix A and notes the following exceptions:

Site Description: Christmas Tree Plantations
The Oryzalin 2G product entry describes a 4 lb a.i./A maximum application rate. [6] However, the Benfluralin RED required that the use rate on this site be reduced to 2 lbs a.i./A. [7] DAS recommends for the Agency to work with this registrant to update this use pattern. Furthermore, DAS recommends that this 4lb/ A use rate not be included in any risk assessment.

Site Desciption: Industrial/ Construction Areas (Outdoor)
The Oryzalin 2G product entry describes a 6 lb a.i./A maximum application rate. [6] However, the Benfluralin RED required that the use rate on this site be reduced to 2 lbs a.i./A. [8] DAS recommends for the Agency to work with this registrant to update this use pattern. Furthermore, DAS recommends that this 6 lb/ A use rate not be included in any risk assessment.

Site Desciption: Non-Agricultural Rights-of-Way/ Fencerows/ Hedgerows, etc.
The Oryzalin 2G product entry [6] describes a 6 lb a.i./A maximum application rate. However, the Benfluralin RED required that the use rate on these sites be reduced to 2 lbs a.i./A. [8] DAS recommends for the Agency to work with this registrant to update this use pattern. Furthermore, DAS recommends that this 6lb/ A use rate not be included in any risk assessment.

Site Desciption: Ornamental Sod Farm (Turf)

Sod was not a specific use pattern that was supported through the re-registration process which culminated in the issuance of the Benfluralin RED. [8] However, three end use products continue to include this sod use pattern: Fertilizer with Starteem ® #1 [9], Fertilizer with Starteem ® #2 [10], and Fertilizer with Starteem ® #3 [11]. DAS recommends for the Agency to work with this registrant to update this use pattern. DAS further recommends that this use pattern should not be included in any risk assessment.

The Agency states on pp. 12 and 33 of 103:
"Benfluralin has a potential for accumulation in aquatic organisms including fish due to the high octanol:water coefficient." (p. 12)

"For mammals, available chronic toxicity data on benfluralin will be used to calculate risk quotients (RQs) for estimated exposures due to bioaccumulation of benfluralin in an aquatic ecosystem." (p. 33)

DAS Comment:
Although DAS agrees that the high K_{ow} value derived for benfluralin might indicate a potential for this substance to bioaccumulate in aquatic organisms, this occurrence is very unlikely to occur in the environment. Under continuous exposure conditions, benfluralin can indeed bioconcentrate, as reflected in a BCF value of 1564 mL/g derived from a fish bioaccumulation study conducted in the laboratory under flow-through conditions [12]. However, once the fish are removed to untreated water, depuration is very rapid with a clearance $t_{1/2}$ of 1.28 days.

Continuous exposure conditions would likely never occur in the environment following agricultural applications due to the rapid dissipation of benfluralin in aquatic systems by photodegradation ($t_{1/2}$ = 5.5-9.9 hrs) and adsorption to sediment (average Koc = 10,750 mL/g). Consequently, under such conditions of transient exposure, any accumulated residues would be quickly cleared from the tissues of aquatic organisms. Such rapid depuration would ensure that significant accumulation would not occur under environmental conditions.

Furthermore, DAS would point out that this rapid depuration would also prevent biomagnification of residues through the food chain from occurring. Predictions of this process are most commonly derived from models based on, and evaluated with, data on highly persistent chemicals that are not readily depurated by aquatic organisms. An example would be the model of Arnot and Gobas, and its derivatives, which were developed using residue data on 64 organochlorine chemicals obtained from organisms collected from the Great Lakes. [13] The substances in question, however, are renowned for being highly recalcitrant and poorly depurated. In our opinion, applying such models to non-persistent and rapidly depurated substances such as benfluralin is not justified. As far as we are aware, no field evidence shows that substances with these properties have ever resulted in significant biomagnification incidents in aquatic food chains, or even bioaccumulation in individual organisms, when products are applied according to Good Agricultural Practice. The use of

such inappropriate and unvalidated models on this type of material, therefore, should be avoided in order to prevent misleading conclusions from being drawn.

The Agency states on page 13 of 103:
A summary of the general chemical and environmental fate properties of benfluralin is presented in Table 3.4.

DAS Comment:
DAS agrees with the Agency summary in Table 3.4 with the following exception:

Parameter: Aerobic Aquatic Metabolism Half-Life (20°C)
The value entry indicates that no data is available. However, an aquatic degradation study is available to address this point. [14] This study was conducted to meet EU German requirements (BBA Guideline Part IV, Section 5-1). The study shows that Benfluralin dissipates from the water/sediment systems with a DT50 value of between 1.1 and 1.3 days (mean 1.2 days). So when applied directly to the water layer of a water/sediment system to mimic entry into aquatic systems via spray drift, benfluralin was either rapidly volatilised or dissipated to the sediment layer with an overall DT_{50} value of *ca* 1.2 days.

The Agency States on Page 17 of 103:
Table 3.7. Benfluralin Concentrations in NAWQA Surface Water Monitoring Program

DAS Comment:
This title appears to be in error. It should likely be changed to "Benfluralin Concentrations in NAWQA Groundwater Monitoring Program.

B. Receptors

The Agency states on pages 23-24 of 103:
A summary of the environmental fate and ecological effects data gaps for benfluralin is listed.

DAS Comment:
GLN 835.1410 – Laboratory Volatility
The Agency states on page 5 of 19 in the document Benfluralin Summary Document that this data requirement is "Non-Guideline." In response to this data requirement, DAS will be submitting a recent study by Knoch and Heim. [15]

GLN 850.1010 – Acute Toxicity Freshwater Invertebrates Study
To address this guideline requirement, DAS submitted the study by Hertl *et al.* on February 12, 2007. [16] According to our records, the EPA evaluation is still pending.

GLN 850.1025 – Oyster Acute Toxicity Test (Shell Disposition)
For the oyster acute toxicity test, DAS disagrees with its inclusion in the data gap summary. Although the study by Hicks [17] has been previously classified as "supplemental" primarily

on the grounds that a specific endpoint has not been identified, DAS believes that this study is of the highest scientific standard and that a repeat study is unlikely to provide the Agency with any useful additional information. Due to the limited solubility of benfluralin in seawater, 50 µg/L was the highest exposure level achievable under flow-through conditions. Measured exposure levels, although lower than target due to adsorption losses, remained essentially constant during the study. All samples were centrifuged prior to analysis and therefore 50 µg/L reflects the maximum functional solubility of benfluralin in seawater. No statistically significant adverse effects on shell growth occurred at this level.

In view of this finding, DAS would propose that a repeat study is considered unnecessary since it would likely only re-confirm that a specific endpoint for inhibition of shell growth is not achievable for benfluralin. Additionally, DAS recommends for the assessment as a data gap for the oyster acute toxicity test (shell disposition) to be reconsidered.

GLN 850.1075 – Fish Acute Toxicity Test (Bluegill, Rainbow Trout)
DAS agrees to provide this study for benfluralin with the bluegill sunfish, *Lepomis macrochirus*, to upgrade the registration package and address these guidelines. DAS looks forward to discussion of the timeline for the conduct and submission of this study.

To address the guideline requirement for the rainbow trout, DAS submitted the study by Hertl *et al.* [18] on February 12, 2007. According to our records, the EPA evaluation is still pending.

GLN 850.1300 – Aquatic Invertebrate Life Cycle (Freshwater)
DAS agrees to provide this study for benfluralin to upgrade the registration package and address these guidelines. DAS looks forward to discussion of the timeline for the conduct and submission of this study.

GLN 850.1500 – Fish Life Cycle
DAS submitted the study by Marino *et al.* [19] on 10/28/2011 to add to the understanding of the chronic effects of benfluralin TGAI on fish. The study was conducted as a 21-day flow-through study on the fathead minnow, *Pimephales promelas*, and was conducted according to US and OECD guidelines for a Fish Short-term Reproduction Assay (OPPTS 890.1350; OECD 2009). According to our records, the EPA evaluation is still pending.

Although not a full life-cycle study, its findings taken together with data from the "core" Early Life Stage study by Cocke [20]are considered sufficient to provide realistic and meaningful data for the evaluation of the chronic effects on fish resulting from exposure to a substance of low persistence in the aquatic environment.

GLN 850.2100 – Avian Acute Oral Toxicity Test (Passerine Species)
DAS agrees to provide this study for benfluralin to upgrade the registration package and address these guidelines. DAS looks forward to discussion of the timeline for the conduct and submission of these studies.

GLN 850.2300 – Avian Reproduction Test (Bobwhite Quail)
For the avian reproduction test, DAS disagrees with its inclusion in the data gap summary. A study by Frey *et al.* [21] was submitted on February 11, 2008 to the Agency to satisfy this data requirement. A subsequent rebuttal to the Agency decision regarding that study by Hudson [22] was submitted to the EPA on August 24, 2010. According to our records, the EPA evaluation is still pending.

GLN 850.4100 – Seedling Emergence Terrestrial Plant Toxicity Test, Tier II
For the seedling emergence terrestrial plant toxicity test tier II, DAS disagrees with its inclusion in the data gap summary. A study by Rockliff [23] was submitted on November 21, 2011 to the Agency to satisfy this data requirement. According to our records, the EPA evaluation is still pending.

GLN 850.4200 – Vegetative Vigor Terrestrial Plant Toxicity Test, Tier II
For the vegetative vigor terrestrial plant toxicity test tier II, DAS disagrees with its inclusion in the data gap summary. A study by Rockliff [24] was submitted on November 21, 2011 to the Agency to satisfy this data requirement. According to our records, the EPA evaluation is still pending.

GLN 850.5400 – Aquatic Plant Growth Tier II Study (Non-Vascular Aquatic Plants)
For the aquatic plant growth Tier II study with non-vascular aquatic plants, DAS disagrees with its inclusion in the data gap summary. The studies by Hancock *et al.* on *Navicula* [25] and *Skeletonema* [26] have been previously classified as "supplemental" on the grounds that "...measured concentrations were below LOQ for all times and treatment groups thus it is not possible to obtain suitable endpoints from the study." [27]

In fact, the measured concentrations for all treatment groups in both studies were above the LOQ and close to nominal on study initiation. Measured levels only fell below LOQ on study termination, as would be expected for a substance such as benfluralin that is rapidly degraded in light. Since algal growth studies, by necessity, must be conducted under conditions of high light intensity, this is an unavoidable feature of the study and should not be taken to invalidate the results. All samples were centrifuged prior to analysis and therefore represent true bio-available concentrations of benfluralin in the exposure media.

DAS believes that these studies are of the highest scientific standard and would propose that a repeat study is considered unnecessary. Additionally, DAS recommends for the assessment as a data gap for the aquatic plant growth Tier II study with non-vascular aquatic plants to be reconsidered.

Furthermore, an equivalent study on *Anabaena flos-aquae*, conducted by Hertl *et al.* [28] was submitted to EPA on February 12, 2007. According to our records, the EPA evaluation is still pending.

40 CFR Part 158 (USEPA, 2007a) – Whole Sediment chronic Invertebrates, Freshwater and Marine

In response to this data requirement, DAS will be submitting the following study: Memmert, U. Effects of Benfluralin Technical on the Development of Sediment-Dwelling Larvae of *Chironomus riparius* in a Water-Sediment System. Study ID: 842140, 2003.

The Agency states on page 27 of 103:

The conceptual model for benfluralin effects on aquatic organisms is described in Figure 6.1.

DAS Comment:

In the Conceptual Model which depicts multiple source inputs to the exposure media, several key factors need to be considered in this scheme.

Spray Drift Input For significant uses, benfluralin is formulated as a granule. Within the Conceptual Model, spray drift could be considered a minor route of exposure for these formulation types.

Runoff Input There are major uses of benfluralin either by soil incorporation or application to turf. Runoff is significantly reduced by soil incorporation since the compound is no longer on the soil surface and thereby unavailable for runoff. Furthermore, turf uses would mitigate runoff since the turf thatch structure significantly reduces runoff. Within the Conceptual Model, runoff could be considered a minor route of exposure for these two uses.

Leaching to Groundwater Input As the sorption K_{oc} value is so high, mobility in soil is considered a low risk for benfluralin. Therefore leaching to groundwater could be considered a minor route of exposure within the Conceptual Model.

Atmospheric Transport Input Although dissipation to air is seen for benfluralin, the photodegradation half-life is very short. In air, benfluralin has calculated photochemical oxidative degradation half-life of 5.8 hours and therefore significant amounts of benfluralin are not expected to be present in air. Therefore atmospheric transport could be considered a minor route of exposure within the Conceptual Model.

C. Analysis Plan

The Agency States on Page 37 of 103:

"EFED recommends that the Pesticide Re-evaluation Division (PRD) request submission of a passerine study protocol for review by the Agency prior to initiation of this study."

DAS Comment:
DAS agrees to provide this study protocol for benfluralin in an effort to upgrade the registration package and address these guidelines. DAS looks forward to discussion of the timeline for the conduct and submission of this protocol.

V. DAS COMMENTS ON THE AGENCY'S HED REVIEW DOCUMENT

The comments are organized in a "point-by-point response" format using the Agency's 19-page review document as the basis. Comments include error correction, requests for clarification, differences in data interpretation, presentation of some additional data, and views regarding the need for new studies as may be appropriate.

The Agency states on page 2 of 19:
"The toxicity database for benfluralin is incomplete at the present time with the exception of a neurotoxicity battery (i.e., acute and subchronic neurotoxicity) and an immunotoxicity study."

DAS Comment:
The statement should be corrected so that it reads: The toxicity database for benfluralin is complete at the present time with the exception of a neurotoxicity battery (i.e., acute and subchronic neurotoxicity) and an immunotoxicity study. As it is currently written, it contradicts a similar statement in the Summary Document on page 7 of 19 which states: *"The toxicity and residue chemistry databases for benfluralin are complete except for the following studies...Acute and Subchronic Neurotoxicity...Immunotoxicity."*

The Agency states on pages 2 and 3 of 19:
"A 28-day inhalation study and a mouse carcinogenicity study were previously required as part of the benfluralin RED Data-Call-In (DCI). These studies have not been submitted to the Agency at this time." (p. 2)

"Previously, the Agency issued a Data-Call-In (DCI) for a 28-day in halation study and a mouse carcinogenicity study. The registrant requested data waivers for these studies: however, they were denied by the Agency (R. Griffin, D294507, 06/08/2004). To date these studies have not yet been submitted." (p. 3)

DAS Comment:
DAS respectfully submits that conduct of a 28-day inhalation study is unnecessary based on the risk assessment conducted by HED for benfluralin in the Benfluralin RED. An assessment was prepared by HED for exposures expected to occur during the 1-30 day time frame of the 28-day inhalation study. Calculated MOEs for this time frame were all well in excess of 1000, indicating that short-term inhalation exposures should not represent a source of concern for workers. As well, the Benfluralin RED required the reduction of application rates to a maximum single rate of 2 lb a.i./A as opposed to the rates of 3, 4 and 6 lbs a.i./A used for

many of the risk assessment calculations. This rate reduction would result in potentially even higher MOEs. DAS believes that the potential risks from inhalation exposure to benfluralin are sufficiently characterized in the results associated with oral systemic studies and in the low acute hazard shown in the Acute Inhalation study.

The Agency states on pages 4 and 12 of 19:
"The Cancer Assessment Review Committee (CARC) classified benfluralin as "Suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential" based on the occurrence of liver tumors in female mice...a mouse carcinogenicity study was required as part of the benfluralin RED process because the doses tested in the males from the available mouse carcinogenicity study were not high enough."(p. 4)

"To date, EPA has not received studies to satisfy the following requirements...Oncogenicity-mouse (870.4200b)." (p. 12)

DAS Comment:
DAS strongly disagrees with the Agency assessment of this requirement as not being satisfied for the mouse oncogenicity study and respectfully requests EPA to reconsider its decision beased on the justifications detailed below.

Justification to support the acceptability of the current study

1) Body weight gain decreases ranging from 8-14% were observed in high dose males and were statistically different when compared to controls for most of the study duration. This is consistent with what is required for an acceptable high dose level as stated in the "Rodent Carcinogenicity Studies: Dose selection and Evaluation" guidance "*for completed carcinogenicity studies, a decrease in body weight or body weight gain approaching 10% in treated animals compared to controls over the duration of the study is an indication that an acceptable dose has been employed.*" [29]

2) The carcinogenicity study in mice was analyzed by the agency and the high dose was deemed an adverse effect level: "LOAEL Males = 185 mg/kg/day (HDT) based on death by mouse urologic syndrome (MUS) (all severities)." [30] [31] In this case, DAS believes that an MTD has been reached based on the increased treatment-related mortality. Indeed, the effects observed in high dose level males satisfy the current USEPA MTD criteria described in the mouse oncogenicity guideline 870.4200 "*The highest dose level in rodents should elicit signs of toxicity without substantially altering the normal life span due to effects other than tumors.*" Therefore, repeating this study in males at a dose level above a dose that is already associated with mortality would only increase the incidence of mortality and potentially invalidate the assessment of carcinogenicity.

3) Mouse urologic syndrome (MUS) though identified as a common finding in certain strains of mice, the incidence rate in high dose males in this mouse carcinogenicity study (30%) was significantly increased when compared to the control males (8.3%) and the historical control incidence rate of 6-24% from the open literature. [32] In addition, seven high dose males died with MUS (~11.6%) when compared to 2 control males (~3.3%) [30]

4) EFSA's assessment of the benfluralin mouse carcinogenicity study: As part of the European Review of benfluralin, Member States and the European Food Safety Authority (EFSA) deemed the study acceptable, stating the following in the their scientific evaluation [33]: "The target organ in mice was the liver, and the combined hepatocellular adenoma/ carcinoma incidence was increased at the LOAEL level of 36 mg/ kg bw/ day. The NOAEL was discussed focusing on equivocal decreased body weight gain during the first year of the study that the rapporteur Member State considered as potentially adverse, however the meeting agreed to set the NOAEL at this low dose level of 6.0 mg/ kg bw/ day."

Justification to refute the need for a new mouse carcinogenicity study

1) The Cancer Assessment Review Committee (CARC) in their evaluation indicated the liver tumors in female mouse to be treatment related and established a NOAEL of 6.9 mg/kg/d for the study based on these liver tumors at the higher dose. [31] The current chronic reference dose was set based on a lower NOAEL (5 mg/kg/d) from the 2-yr chronic rat study. [34] Therefore, a repeat study in male mice at a new high dose level could not influence established NOAELs or Reference Doses for the molecule and hence could not bring any value to human health-based risk assessments.

2) Structure-Activity Relationship (SAR): Benfluralin belongs to the dinitroaniline (DNA) class of herbicides which also includes oryzalin, trifluralin, pendimethalin, and ethalfluralin. The available mouse carcinogenicity studies on these molecules did not induce increases in tumor incidence in case but consistently identified liver as the target organ. [35] [36] [37] [38] This point strengthens the position that conduct of a new mouse study with benfluralin is unlikely to provide any valuable new information and is not warranted.

3) Non-relevance of liver tumors to humans: Liver was identified as benfluralin's primary target organ in mouse and rat chronic studies. [30] [39] DAS designed and conducted a study to evaluate the liver (and also thyroid tumor) mode of action (MOA) in rats. [40] [41] The study demonstrated that like Phenobarbital, its effects on the liver are mediated via CAR, which is considered of limited to no relevant to humans due to quantitative and qualitative differences in in response between humans and rodents. DAS believes that benfluralin would operate via the same MOA on rodent liver (rats and mice). In this case, even if a new mouse carcinogencity study at a higher dose level in males were feasible, it is most likely to lead to liver tumors mediated by a CAR MOA of little to no relevance to humans. In this case, there would be no justification or value in such as study.

4) Value added by repeat studies in male mice: Billington *et al.* published a paper evaluating the value added by mouse carcinogenicity studies in assessing the risk to humans and stated that: "Assessment of 202 pesticides from the European Union review programme under Directive 91/411/EEC indicated that the moue carcinogenicity study contributed little or nothing to either derivation of an acceptable daily intake (ADI) for assessment of chronic risk to humans, or hazard classification for labeling purposes." [42] Similarly, there are reports to show that testing of a chemical in male rats and female mice only is sufficient to detect 90% or more of potential carcinogens. [43] [44] [45] Thus, repeating studies in female rats or male mice may contribute little to no additional information on the carcinogenic potential of a pesticide.

5) Finally, for reasons of animal welfare and the 3R's (Replacement, Refinement and Reduction) encouraged by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), the conduct of a new study involving the use of up to 200 animals is not justified.

Request for reconsideration:
In summary, the mouse carcinogenicity study met the USEPA criteria for an MTD and was recently deemed acceptable by other regulatory authorities in Europe. Acceptable Reference Doses have been set by EPA whereby a new study could not influence established risk assessments. EPA reviews of related DNAs indicate that they are not carcinogenic in mice at acceptable high dose levels. The liver is the primary target organ for benfluralin in rodents and a CAR-mediated MOA has been determined whereby even if a repeat study at a new high dose level in males were feasible, which DAS disputes, liver tumors of little to no relevance to humans would be the most likely outcome. From a scientific and an animal welfare perspective, a repeat study is not justified.

DAS concludes that the risks posed by benfluralin can be fully addressed through the existing studies available and respectfully requests EPA to reconsider its recent position to require a second carcinogenicity study in male mice.

The Agency states on page 7 of 19:
"An unrefined chronic dietary (food only) risk assessment was completed for the benflurlain RED...." (p. 7)

"The Screening Concentration in Groundwater (SCI-GROW) model was utilized to estimate the concentration of benflurlain...." (p. 7)

DAS Comment:
The name of the active ingredient is misspelled in two places on this page. Please correct it so that it reads: benfluralin.

The Agency states on page 12 of 19:

"HED does not anticipate that additional residue chemistry, toxicology or occupational/ residential exposure data will be required for the benfluralin registration review process, with the exception of the following studies listed below:

- *Immunotoxicity Study (OPPTS 870.7800); and*
- *Neurotoxicity Battery for Ethalfluralin (Acute and Subchronic Studies) (OPPTS 870.6200)"*

DAS Comment:

Immunotoxicity

In accordance with the revised 40 CFR part 158 toxicological data requirement, an immunotoxicity study has been requested for the registration review of benfluralin. Based on the available toxicity data from the repeat dose studies, benfluralin does not appear to present any immunotoxicity hazard. In addition, an industry effort in cooperation with US EPA currently is underway to evaluate the impact of this data requirement on the risk assessment. Consequently, DAS recommends the need for the immunotoxicity study for benfluralin to be reconsidered.

Neurotoxicity

In accordance with the revised 40 CFR part 158 toxicological data requirement, a neurotoxicity battery has been requested for the registration review of benfluralin. Based on the available toxicity data from the single and repeat dose studies, benfluralin does not appear to present any neurotoxicity hazard. In addition, upon review of the use pattern of this active ingredient and the exposure assessments (including worker exposure), the potential for human exposure is identified to be very low. Based on these observations, DAS recommends the need for the neurotoxicity battery for benfluralin to be reconsidered.

VI. REFERENCES

[1] Docket ID Number: EPA-HQ-OPP-2011-0931-0002, www.regulations.gov.

[2] Docket ID Number: EPA-HQ-OPP-2011-0931-0003, www.regulations.gov.

[3] Docket ID Number: EPA-HQ-OPP-2011-0931-0004, www.regulations.gov.

[4] Balan DF is a registered product of Loveland Products, Inc., EPA Reg No. 34704-746.

[5] U.S. Environmental Protection Agency. (2004): Reregistration Eligibility Decision (RED) for Benfluralin, Office of Prevention, Pesticides, and Toxic Substances, Washington, D.C. EPA 738-R-04-012. July 2004, pp. 74-75.

[6] Oryzalin 2G is a registered product of Control Solutions, Inc., EPA Registration No. 53883-220.

[7] Benfluralin RED p. 74.

[8] Benfluralin RED p. 75.

[9] Fertilizer with Starteem ® #1is a registered trademark of Harrell's, LLC, EPA Reg. No. 52287-10.

[10] Fertilizer with Starteem ® 21is a registered trademark of Harrell's, LLC, EPA Reg. No. 52287-11.

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[19] **MRID 48614906**. Marino, T. *et al.* Benefin: A Fish Short-Term Reproduction Assay Using the Fathead Minnow, *Pimephales promelas*. Study ID: 101165, 2011.

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[22] **MRID 48204501**. Hudson, A. Response to Wagman and Bailey DER of December 28, 2009 (DP Barcode: 352.183); Benfluralin: A Reproduction Study with the Northern Bobwhite. (2010): (EPA MRID: 47346601). Study ID: AKH082310, 2010.

[23] **MRID 48665102**. Rockliff, C. Evaluation of the Phytotoxicity of Benfluralin (GF-2436, 600 g as/kg, WG). GLP Seedling Emergence and Seedling Growth. Study ID: 091016.

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